

BL

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
3 April 2003 (03.04.2003)

PCT

(10) International Publication Number
WO 03/026648 A1

(51) International Patent Classification⁷: A61K 31/415,
C07D 231/06, 401/12, A61K 31/4155, 31/4725, C07D
401/04

CP Weesp (NL). VAN STUIVENBERG, Herman, H.
[NL/NL]; Solvay Pharmaceuticals B.V., c/o C.J. van
Houtenlaan 36, NL-1381 CP Weesp (NL).

(21) International Application Number: PCT/EP02/10435

(74) Agent: MUIS, Maarten; OCTROOIBUREAU ZOAN
B.V., P.O. Box 140, NL-1380 AC Weesp (NL).

(22) International Filing Date:

17 September 2002 (17.09.2002)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

01203849.3 21 September 2001 (21.09.2001) EP

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG,
SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ,
VC, VN, YU, ZA, ZM, ZW.

(71) Applicant (*for all designated States except US*): SOLVAY
PHARMACEUTICALS B.V. [NL/NL]; C.J. van Houten-
laan 36, NL-1381 CP Weesp (NL).

(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK,
TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
GW, ML, MR, NE, SN, TD, TG).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): KRUSE, Cornelis,
G. [NL/NL]; Solvay Pharmaceuticals B.V., c/o C.J. van
Houtenlaan 36, NL-1381 CP Weesp (NL). LANGE, Jose-
phus, H.M. [NL/NL]; Solvay Pharmaceuticals B.V., c/o
C.J. van Houtenlaan 36, NL-1381 CP Weesp (NL). TIP-
KER, Jacobus [NL/NL]; Solvay Pharmaceuticals B.V.,
c/o C.J. van Houtenlaan 36, NL-1381 CP Weesp (NL).
HERREMANS, Arnoldus, H.J. [NL/NL]; Solvay Phar-
maceuticals B.V., c/o C.J. van Houtenlaan 36, NL-1381

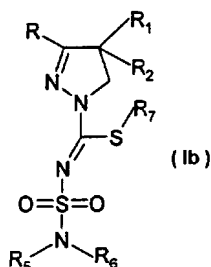
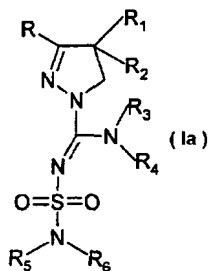
Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

WO 03/026648 A1

(54) Title: 4,5-DIHYDRO-1H-PYRAZOLE DERIVATIVES HAVING POTENT CB₁-ANTAGONISTIC ACTIVITY



(57) Abstract: The present invention relates to a group of novel 4,5-dihy-
dro-1H-pyrazole derivatives which are potent cannabinoid (CB₁) receptor
antagonists with utility for the treatment of diseases connected with disor-
ders of the cannabinoid system. The compounds have the general formula
(1a) or (1b) wherein the symbols have the meanings given in the specifi-
cation. The invention also relates to methods for the preparation of these
compounds, and to pharmaceutical compositions containing one or more of
these compounds as an active component.

4,5-Dihydro-1H-pyrazole derivatives having potent CB₁-antagonistic activity

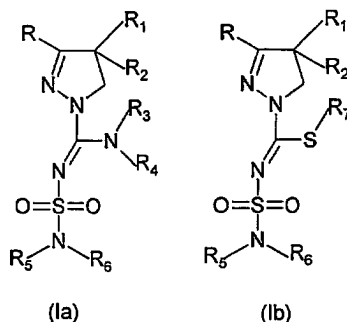
5 The present invention relates to a group of novel 4,5-dihydro-1H-pyrazole derivatives, to methods for the preparation of these compounds, and to pharmaceutical compositions containing one or more of these compounds as an active component.

The above mentioned 4,5-dihydro-1H-pyrazoles are potent cannabinoid (CB₁) receptor antagonists with utility for the treatment of disorders involving cannabinoid neurotransmission.

10

Cannabinoids are present in the Indian hemp *Cannabis sativa* and have been used as medicinal agents for centuries (Mechoulam, R. and Feigenbaum, J.J. *Prog. Med. Chem.* **1987**, 24, 159). However, only within the past ten years the research in the cannabinoid area has revealed pivotal information on cannabinoid receptors and their
15 (endogenous) agonists and antagonists. The discovery and the subsequent cloning of two different subtypes of cannabinoid receptors (CB₁ and CB₂) stimulated the search for novel cannabinoid receptor antagonists (Munro, S. *et al.*, *Nature* **1993**, 365, 61. Matsuda, L.A. and Bonner, T.I. *Cannabinoid Receptors*, Pertwee, R.G. Ed. **1995**, 117, Academic Press, London). In addition, pharmaceutical companies
20 became interested in the development of cannabinoid drugs for the treatment of diseases connected with disorders of the cannabinoid system (Consroe, P. *Neurobiology of Disease* **1998**, 5, 534. Pop, E. *Curr. Opin. In CPNS Investigational Drugs* **1999**, 1, 587. Greenberg, D.A. *Drug News Perspect.* **1999**, 12, 458. Pertwee, R.G., *Progress in Neurobiology* **2001**, 63, 569). Hitherto, several CB₁ receptor
25 antagonists are known. Sanofi disclosed their diarylpyrazole congeners as selective CB₁ receptor antagonists. A representative example is SR-141716A (Dutta, A.K. *et al.*, *Med. Chem. Res.* **1994**, 5, 54. Lan, R. *et al.*, *J. Med. Chem.* **1999**, 42, 769. Nakamura-Palacios, E.M. *et al.*, *CNS Drug Rev.* **1999**, 5, 43). CP-272871 is a pyrazole derivative, like SR141716A, but less potent and less CB₁ receptor subtype-
30 selective than SR141716A (Meschler, J.P. *et al.*, *Biochem. Pharmacol.* **2000**, 60, 1315). Aminoalkylindoles have been disclosed as CB₁ receptor antagonists. A representative example is Iodopravadoline (AM-630), which was introduced in 1995. AM-630 is a moderately active CB₁ receptor antagonist, but sometimes behaves as a weak partial agonist (Hosohata, K. *et al.*, *Life Sc.* **1997**, 61, PL115). Researchers
35 from Eli Lilly described aryl-aryl substituted benzofurans as selective CB₁ receptor antagonists (e.g. LY-320135) (Felder, C.C. *et al.*, *J. Pharmacol. Exp. Ther.* **1998**, 284, 291). 3-Alkyl-5,5'-diphenylimidazolidinediones were described as cannabinoid receptor ligands, which were indicated to be cannabinoid antagonists (Kanyonyo, M. *et al.*, *Biorg. Med. Chem. Lett.* **1999**, 9, 2233). Aventis Pharma claimed
40 diarylmethyleneazetidine analogs as CB₁ receptor antagonists (Mignani, S. *et al.*, Patent FR 2783246, 2000; *Chem. Abstr.* **2000**, 132, 236982). Tricyclic pyrazoles were claimed by Sanofi-Synthelabo as CB₁ antagonists (Barth, F. *et al.*, Patent WO 0132663, 2001; *Chem. Abstr.* **2001**, 134, 340504). Interestingly, many CB₁ receptor

- antagonists have been reported to behave as inverse agonists *in vitro* (Landsman, R.S. *et al.*, *Eur. J. Pharmacol.* **1997**, 334, R1). Reviews provide a nice overview of the cannabinoid research area (Mechoulam, R. *et al.*, *Prog. Med. Chem.* **1998**, 35, 199. Lambert, D.M. *Curr. Med. Chem.* **1999**, 6, 635. Mechoulam, R. *et al.*, *Eur. J. Pharmacol.* **1998**, 359, 1. Williamson, E.M. and Evans, F.J. *Drugs* **2000**, 60, 1303.
- 5 Pertwee, R.G. *Addiction Biology* **2000**, 5, 37. Robson, P. *Br. J. Psychiatry* **2001**, 178, 107. Pertwee, R. G. *Prog. Neurobiol.* **2001**, 63, 569. Goya, P and Jagerovic, N. *Exp. Opin. Ther. Patents* **2000**, 10, 1529. Pertwee, R. G. *Gut* **2001**, 48, 859).
- 10 It has now surprisingly been found that potent and selective antagonism of cannabinoid-CB₁ receptors is present in the novel 4,5-dihydro-1H-pyrazole derivatives of the formula (Ia) or (Ib), prodrugs thereof, tautomers thereof and salts thereof



15

wherein

- R and R₁ independently represent phenyl, thienyl or pyridyl which groups may be substituted with 1, 2 or 3 substituents Y, which can be the same or different, from the group C₁₋₃-alkyl or alkoxy, hydroxy, halogen, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, nitro, amino, mono- or dialkyl (C₁₋₂)-amino, mono- or dialkyl (C₁₋₂)-amido, (C₁₋₃)-alkyl sulfonyl, dimethylsulfamido, C₁₋₃-alkoxycarbonyl, carboxyl, trifluoromethylsulfonyl, cyano, carbamoyl, sulfamoyl and acetyl, or R and/or R₁ represent naphthyl,
- 20 - R₂ represents hydrogen, hydroxy, C₁₋₃-alkoxy, acetyloxy or propionyloxy,
- R₃ represents a hydrogen atom or a branched or unbranched C₁₋₈ alkyl group or a C₃₋₇ cycloalkyl group which alkyl group or cycloalkyl group may be substituted with a hydroxy group,
- 25 - R₄ represents a hydrogen atom or a branched or unbranched C₁₋₈ alkyl, C₃₋₈ cycloalkyl, C₂₋₁₀ heteroalkyl, C₃₋₈ nonaromatic heterocycloalkyl or C₄₋₁₀ nonaromatic heterocycloalkyl-alkyl moiety which moieties may contain one or more heteroatoms from the group (O, N, S), which moieties may be substituted with a keto group, trifluoromethyl group, C₁₋₃ alkyl group, hydroxy, amino, monoalkylamino, or dialkylamino group or a fluoro atom, or R₄ represents an
- 30 amino, hydroxy, phenoxy or benzyloxy group or R₄ represents a branched or
- 35

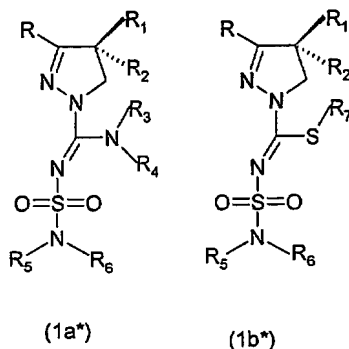
- unbranched C₁₋₈ alkoxy, C₃₋₈ alkenyl, C₅₋₈ cycloalkenyl or C₆₋₉ cycloalkenylalkyl group which groups may contain a sulphur, nitrogen or oxygen atom, a keto group or -SO₂- group which C₁₋₈ alkoxy, C₃₋₈ alkenyl, C₅₋₈ cycloalkenyl or C₆₋₉ cycloalkenylalkyl groups may be substituted with a hydroxy group, a trifluoromethyl group, an amino group, a monoalkylamino group or dialkylamino group or a fluoro atom, or R₄ represents a phenyl, benzyl, pyridyl, thienyl, pyridylmethyl or phenethyl group wherein the aromatic rings may be substituted with 1, 2 or 3 of the substituents Y, wherein Y has the meaning as indicated above, or
- R₄ represents a group NR₈R₉ with the proviso that R₈ represents a hydrogen atom or a methyl group and wherein R₈ and R₉ are the same or different and represent C₁₋₄ alkyl or C₂₋₄ trifluoroalkyl or R₈ and R₉ - together with the nitrogen atom to which they are bonded - form a saturated or un-saturated heterocyclic moiety having 4 to 8 ring atoms which heterocyclic moiety may contain an oxygen or sulphur atom or a keto group or -SO₂- group or an additional nitrogen atom, which saturated or unsaturated heterocyclic moiety may be substituted with a C₁₋₄ alkyl group or
- R₃ and R₄ - together with the nitrogen atom to which they are bonded - form a saturated or unsaturated, monocyclic or bicyclic heterocyclic moiety having 4 to 10 ring atoms, which heterocyclic moiety may contain one or more atoms from the group (O, N, S) or a keto group or -SO₂- group, which moiety may be substituted with a C₁₋₄ alkyl, hydroxyalkyl, phenyl, thienyl, pyridyl, amino, monoalkylaminoalkyl, dialkylaminoalkyl, monoalkylamino, dialkylamino, aminoalkyl, azetidiny, pyrrolidiny, piperidiny or hexahydro-1H-azepiny group,
- R₅ and R₆ independently of each other represent a hydrogen atom or a branched or unbranched C₁₋₈ alkyl or alkenyl group which groups may contain one or more heteroatoms from the group (O, N, S), a keto group or a -SO₂- group and which groups may be substituted with a hydroxy or amino group, or R₅ and R₆ independently of each other represent a C₃₋₈ cycloalkyl group or C₃₋₈ cycloalkenyl group which may contain one or more ring heteroatoms from the group (O, N, S) or the -SO₂- group and which groups may be substituted with a hydroxy group, alkyl (C₁₋₃), the -SO₂- group, the keto group, amino group, monoalkylamino group (C₁₋₃) or dialkylamino group (C₁₋₃), or
- R₅ represents a naphthyl group or a phenyl group which phenyl group may be substituted with 1, 2 or 3 substituents Y wherein Y has the meaning as described hereinabove, with the proviso that R₆ represents a hydrogen atom, or a branched or unbranched alkyl group (C₁₋₅) which alkyl group may contain one or more heteroatoms from the group (O, N, S) or the -SO₂- group and which alkyl group may be substituted with a hydroxy, keto or amino group, or
- R₅ and R₆ - together with the nitrogen atom to which they are bonded - form a monocyclic, bicyclic or tricyclic alkyl or alkenyl group which may contain ring heteroatoms from the group (O, N, S), the keto or the SO₂ group and which

monocyclic, bicyclic or tricyclic alkyl or alkenyl group may be substituted with a hydroxy group, alkyl (C_{1-3}) group, SO_2 group, keto group, amino group, monoalkylamino group (C_{1-3}), dialkylamino group

(C_{1-3}), pyrrolidinyl group or piperidinyl group, which monocyclic, bicyclic or tricyclic alkyl or alkenyl group may contain an annelated phenyl group which annelated phenyl group may be substituted with 1 or 2 substituents Y, wherein Y has the meaning as described herein above,

– R_7 represents branched or unbranched C_{1-3} alkyl.

- 10 At least one centre of chirality is present (at the C_4 position of the 4,5-dihydro-1H-pyrazole moiety) in the compounds of the formula (Ia) and (Ib). The invention relates both to racemates, mixtures of diastereomers and the individual stereoisomers of the compounds having formula (Ia) or (Ib). Particular compounds of interest of formula (Ia) or (Ib) have the absolute stereoconfiguration at the C_4 position of the 4,5-dihydro-1H-pyrazole moiety as represented by the formulas (1a*) and (1b*):



The invention also relates both to the E isomer, Z isomer and E/Z mixtures of compounds having formula (Ia) or (Ib).

20

The compounds of the invention can be brought into forms suitable for administration by means of usual processes using auxiliary substances and/or liquid or solid carrier materials.

25

Due to the potent CB_1 antagonistic activity the compounds according to the invention are suitable for use in the treatment of psychiatric disorders such as psychosis, anxiety, depression, attention deficits, memory disorders, cognitive disorders, appetite disorders, obesity, addiction, appetite, drug dependence and neurological disorders such as neurodegenerative disorders, dementia, dystonia, muscle spasticity, tremor, epilepsy, multiple sclerosis, traumatic brain injury, stroke, Parkinson's disease, Alzheimer's disease, epilepsy, Huntington's disease, Tourette's syndrome, cerebral ischaemia, cerebral apoplexy, craniocerebral trauma, stroke, spinal cord injury, neuroinflammatory disorders, plaque sclerosis, viral encephalitis, demyelination related disorders, as well as for the treatment of pain disorders,

30

including neuropathic pain disorders, and other diseases involving cannabinoid neurotransmission, including the treatment of septic shock, glaucoma, cancer, diabetes, emesis, nausea, asthma, respiratory diseases, gastrointestinal disorders, gastric ulcers, diarrhoea and cardiovascular disorders.

5

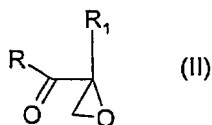
The affinity of the compounds of the invention for cannabinoid CB₁ receptors was determined using membrane preparations of Chinese hamster ovary (CHO) cells in which the human cannabinoid CB₁ receptor is stably transfected in conjunction with [³H]CP-55,940 as radioligand. After incubation of a freshly prepared cell membrane
10 preparation with the [³H]-ligand, with or without addition of compounds of the invention, separation of bound and free ligand was performed by filtration over glassfiber filters. Radioactivity on the filter was measured by liquid scintillation counting.

15 The cannabinoid CB₁ antagonistic activity of compounds of the invention was determined by functional studies using CHO cells in which human cannabinoid CB₁ receptors are stably expressed. Adenylyl cyclase was stimulated using forskolin and measured by quantifying the amount of accumulated cyclic AMP. Concomitant activation of CB₁ receptors by CB₁ receptor agonists (e.g. CP-55,940 or (R)-WIN-
20 55,212-2) can attenuate the forskolin-induced accumulation of cAMP in a concentration-dependent manner. This CB₁ receptor-mediated response can be antagonised by CB₁ receptor antagonists such as the compounds of the invention.

Intermediates having formula (II) (see below) can be obtained according to methods known, for example: a) Francotte, E.; Tong, Z. *Chem. Abstr.* **126**, 213598; b) Rempfler, H. and Kunz, W. *Chem. Abstr.* **113**, 40432; c) Rempfler, H. and Kunz, W. *Chem. Abstr.* **107**, 217473.

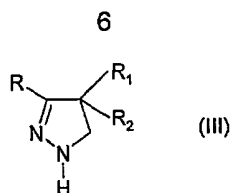
Intermediates having formula (III) wherein R₂ represents hydrogen (see below) can be obtained according to methods known, for example: a) EP 0021506; b) DE
30 2529689, c) Grosscurt, A.C. et al., *J. Agric. Food Chem.* **1979**, 27, (2), 406.

Intermediates having formula (III) wherein R₂ represents a hydroxy group can be obtained by reacting a compound having formula (II) with hydrazine or hydrazine hydrate



35

This reaction, preferably carried out in an organic solvent such as ethanol, yields a compound having formula (III) wherein R₂ represents a hydroxy group.

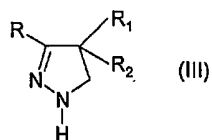


Suitable synthetic routes for the compounds of the invention are the following:

5

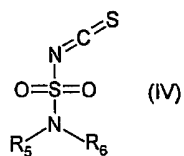
Synthetic route A

Step 1: reaction of a compound having formula (III)

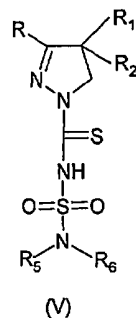


10

with a compound having formula (IV).

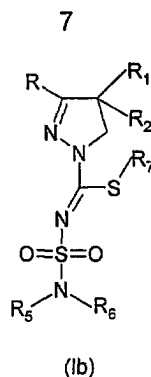


- 15 This reaction is preferably carried out in an organic solvent, such as for example dichloromethane, and yields a compound having formula (V) wherein R, R₁, R₂, R₅ and R₆ have the meaning as described above for compound (Ia), and which are new.



20

Step 2: reaction of a compound having formula (V) with a compound R₇-X, wherein X represents a leaving group, for example an iodide group, and R₇ has the meaning as described above for (Ib) gives a compound having formula (Ib).



This reaction is preferably carried out in the presence of a base, for example triethylamine.

5

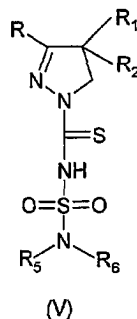
Step 3: reaction of a compound having formula (Ib) with an amine having formula HNR_3R_4 wherein R_3 and R_4 have the meanings as described above, analogous to the method described in *Synth. Commun.* **1996**, 26, (23), 4299.

This reaction gives a compound having formula (Ia).

10

Synthetic route A1

Step 1: Reaction of a compound having formula (V)



15

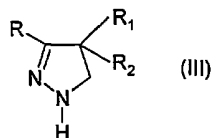
with an amine having formula HNR_3R_4 wherein R_3 and R_4 have the meanings as described above in the presence of a mercury(II) salt, for example HgCl_2 , gives a compound having formula (Ia).

20

This reaction is preferably carried out in an organic solvent, such as for example acetonitrile, analogous to the method described in *Synth. Commun.* **1996**, 26, (23), 4299.

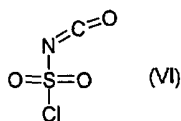
Synthetic route A2

Step 1: reaction of a compound having formula (III)



5

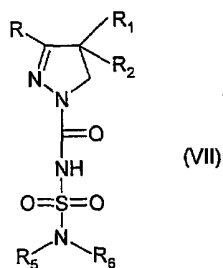
with a isocyanate derivative having formula (VI), followed by treatment with an amine HNR_5R_6



10

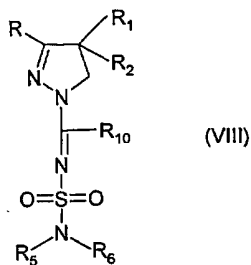
This reaction is preferably carried out in an organic solvent like dichloromethane, and yields a compound having formula (VII). Compounds having formula (VII) wherein R, R₁, R₂, R₅ and R₆ have the meaning as described herein above for compound (Ia) are new.

15



Step 2: reaction of a compound having formula (VII) with a halogenating agent, such as for example PCl_5 , gives a compound having formula (VIII)

20



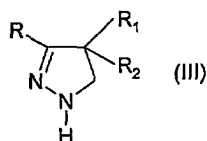
wherein R_{10} represents a halogen atom, for example a chloro atom. This reaction is preferably carried out in an organic solvent such as chlorobenzene.

Compounds having formula (VIII) wherein R , R_1 , R_2 , R_5 and R_6 have the meanings as described above for compound (Ia) and wherein R_{10} represents a halogen atom, are new.

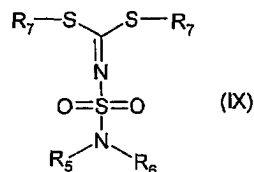
Step 3: reaction, preferably carried out in an inert organic solvent such as dichloromethane, of a compound having formula (VIII) with an amine having formula HNR_3R_4 wherein R_3 and R_4 have the meanings as described above gives a compound having formula (Ia).

Synthetic route A3

Step 1: reaction of a compound having formula (III)



with a compound having formula (IX)



gives a compound having formula (Ib), (see e.g. *Chem. Ber.* **1966**, 99, 2885 and *Chem. Ztg.* **1984**, 108, (12), 404).

The preparation of the compounds is illustrated in the following examples.

Example 1

3-(4-Chlorophenyl)-N'-(((ethyl)propylamino)sulfonyl)-N-methyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine

Part A: To a stirred solution of ((ethyl)propylamino)sulfonyl isothiocyanate (5.98 gram, 25.4 mmol) in dry dichloromethane in a nitrogen atmosphere is added of 3-(4-chlorophenyl)-4-phenyl-4,5-dihydro-1H-pyrazole (6.52 gram, 25.4 mmol). After stirring for 90 minutes the resulting solution is concentrated *in vacuo* and purified by column chromatography (CH_2Cl_2 , silicagel, $R_f \sim 0.45$). The resulting solid is recrystallized from diethyl ether to give 3-(4-chlorophenyl)-N-

(((ethyl)propylamino)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-thiocarboxamide (6.57 gram, 56 % yield). Melting point: 144-146 °C.

Part B: To a stirred suspension of 3-(4-chlorophenyl)-N-(((ethyl)propylamino)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-thiocarboxamide (2.32 gram, 5 mmol) in acetonitrile (20 mL) is added cold methylamine (4 mL). To the resulting solution is added a solution of HgCl₂ (1.5 gram) in acetonitrile (10 mL). The resulting black suspension is stirred for four hours. The precipitate is removed by filtration. The filtrate is concentrated *in vacuo*, dissolved in dichloromethane and successively washed with aqueous 0.5 N NaOH solution and water, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The resulting oil is crystallized from diethyl ether to give 3-(4-chlorophenyl)-N'-(((ethyl)propylamino)sulfonyl)-N-methyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine (1.78 gram, 77 % yield). Melting point (MP): 129-131 °C.

In an analogous manner the compounds having formula (Ia) listed below have been prepared:

2. 3-(4-Chlorophenyl)-N'-(((ethyl)methylamino)sulfonyl)-N-methyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 112-115 °C.
- 20 3. 3-(4-Chlorophenyl)-N'-((diethylamino)sulfonyl)-N-(2-hydroxyethyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 104-106 °C.
4. 3-(4-Chlorophenyl)-N-(2-hydroxyethyl)-N'-((piperidin-1-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MS (ESI+): 490 (MH⁺).
5. 3-(4-Chlorophenyl)-N'-((diethylamino)sulfonyl)-N-(2-(morpholin-4-yl)ethyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MS (ESI+): 547 (MH⁺)
- 25 6. 3-(4-Chlorophenyl)-N'-((dimethylamino)sulfonyl)-N-(2-(morpholin-4-yl)ethyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. Amorphous.
7. 3-(4-Chlorophenyl)-N'-((diethylamino)sulfonyl)-N-(2-(dimethylamino)ethyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MS (ESI+): 505 (MH⁺).
- 30 8. 3-(4-Chlorophenyl)-N-(3-(dimethylamino)propyl)-N'-((dimethylamino)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. Amorphous.
9. 3-(4-Chlorophenyl)-N-(2-(piperidin-1-yl)ethyl)-N'-((piperidin-1-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MS (ESI+): 557 (MH⁺).
10. 3-(4-Chlorophenyl)-N-(2-(morpholin-4-yl)ethyl)-N'-((piperidin-1-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MS (ESI+): 559 (MH⁺); MP: 174-176 °C.
- 35 11. 3-(4-Chlorophenyl)-N-(2-(dimethylamino)ethyl)-N'-((dimethylamino)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. Amorphous.
12. 3-(4-Chlorophenyl)-N-(2-(diethylamino)ethyl)-N'-((dimethylamino)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. Amorphous.
- 40 13. 3-(4-Chlorophenyl)-N-(3-(dimethylamino)propyl)-N'-((diethylamino)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MS (ESI+): 519 (MH⁺).

14. 3-(4-Chlorophenyl)-N-(2-(diethylamino)ethyl)-N'-((diethylamino)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidinium hemifumarate. MP: 182-185 °C.
15. 3-(4-Chlorophenyl)-N-(2-(dimethylamino)ethyl)-N'-((piperidin-1-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidinium. Amorphous.
- 5 16. 3-(4-Chlorophenyl)-N-(2-(diethylamino)ethyl)-N'-((pyrrolidin-1-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidinium. Amorphous.
17. 3-(4-Chlorophenyl)-N'-((diethylamino)sulfonyl)-N-(1-methylpiperidin-4-yl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidinium. Amorphous.
18. 3-(4-Chlorophenyl)-N'-((dimethylamino)sulfonyl)-N-(2-hydroxyethyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidinium. MP: 123-126 °C.
- 10 19. 3-(4-Chlorophenyl)-N'-((diethylamino)sulfonyl)-N-methyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidinium. Amorphous. $R_f \sim 0.4$ (diethyl ether).
20. 3-(4-Chlorophenyl)-N'-(((ethyl)propylamino)sulfonyl)-N-Methyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidinium. MP: 129-131 °C.
- 15 21. 3-(4-Chlorophenyl)-N-methyl-N'-((pyrrolidin-1-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidinium. Amorphous. $R_f \sim 0.3$ (MTBE).
22. 3-(4-Chlorophenyl)-N-methyl-N'-(((methyl)propylamino)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidinium. MP: 132-134 °C.
23. 3-(4-Chlorophenyl)-N,N-dimethyl-N'-((pyrrolidin-1-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidinium. Amorphous. $R_f \sim 0.25$ (MTBE).
- 20 24. 3-(4-Chlorophenyl)-N-methyl-N'-((piperidin-1-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidinium. MP: 175-177 °C.
25. 3-(4-Chlorophenyl)-N'-((hexahydro-1H-azepin-1-yl)sulfonyl)-N-methyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidinium. Amorphous.
- 25 26. 3-(4-Chlorophenyl)-N'-((dipropylamino)sulfonyl)-N-methyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidinium. MP: 141-142 °C.
27. 3-(4-Chlorophenyl)-N'-(((isopropyl)methylamino)sulfonyl)-N-methyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidinium. MP: 134-136 °C.
28. 3-(4-Chlorophenyl)-N-methyl-N'-((octahydroazocin-1-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidinium. MP: 165-168 °C.
- 30 29. 3-(4-Chlorophenyl)-N-ethyl-N'-((piperidin-1-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidinium. Amorphous.
30. 3-(4-Chlorophenyl)-N'-((dimethylamino)sulfonyl)-N-methyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidinium. MP: 166-168 °C.

35

Example 31**3-(4-Chlorophenyl)-N'-((dimethylamino)sulfonyl)-N-propyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidinium**

Part A: To a stirred solution of chlorosulfonyl isocyanate (1.73 mL, 20 mmol) in dry dichloromethane (20 mL) is very slowly added a solution of 3-(4-chlorophenyl)-4-phenyl-4,5-dihydro-1H-pyrazole (5.13 gram, 20 mmol) in dry dichloromethane (125 mL) at -5 °C. After stirring for 30 minutes the reaction mixture is allowed to attain

40

room temperature and stirred for another 2 hours. After cooling to 0 °C liquid dimethylamine (5 mL) is added and the resulting solution is stirred for another hour at 0 °C and for 2 hours at room temperature. The solution is washed with water, filtered over hyflo and concentrated *in vacuo*. Flash chromatography (MTBE, $R_f \sim 0.3$) gives
5 3-(4-chlorophenyl)-N-((dimethylamino)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamide (4.75 g, 58 %). MP: 210-212 °C.

Part B: A mixture of 3-(4-chlorophenyl)-N-((dimethylamino)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamide (1.47 gram, 3.62 mmol) and phosphorus pentachloride (0.80 gram, 3.84 mmol) in chlorobenzene (20 mL) is heated at reflux
10 temperature for 1 hour. After thorough concentration *in vacuo*, the formed 3-(4-chlorophenyl)-N-((dimethylamino)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboximidoyl chloride is suspended in dry dichloromethane and reacted with cold *n*-propylamine (1.0 mL) at 0 °C. After stirring for 1 hour, the mixture is dissolved in ethyl acetate and washed with water and concentrated *in vacuo*. The residue is purified by
15 column chromatography (dichloromethane/acetone = 19/1 (v/v), $R_f \sim 0.35$) to give an oil (0.82 g). Crystallisation from diethyl ether, followed by recrystallisation from ethanol gives 3-(4-chlorophenyl)-N'-((dimethylamino)sulfonyl)-N-propyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboximidine (0.38 gram, 23 % yield). MP: 127-129°C.

20 In an analogous manner the compounds having formula (Ia) listed below have been prepared:

32. 3-(4-Chlorophenyl)-N'-((dimethylamino)sulfonyl)-N-(2-fluoroethyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboximidine. MP: 128-131 °C.

25 33. 3-(4-Chlorophenyl)-N'-((dimethylamino)sulfonyl)-4-phenyl-N-(2,2,2-trifluoroethyl)-4,5-dihydro-1H-pyrazole-1-carboximidine. MP: 158-159 °C.

34. 3-(4-Chlorophenyl)-N'-((dimethylamino)sulfonyl)-N-methoxy-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboximidine. MP: 170-172 °C.

30 Example 35

3-(4-Chlorophenyl)-N-((piperidin-1-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester

Part A: To a stirred solution of (piperidin-1-yl)sulfonyl isothiocyanate (54.77 g, 266 mmol) in dry dichloromethane (900 mL) in a nitrogen atmosphere is added 3-(4-chlorophenyl)-4-phenyl-4,5-dihydro-1H-pyrazole (68.3 gram, 266 mmol). After stirring
35 for 16 hours an additional amount of dichloromethane is added. The resulting solution is twice washed with water, dried over Na₂SO₄, and concentrated *in vacuo*. After addition of MTBE, the residue crystallizes. The crystalline material is collected and washed with MTBE to give 3-(4-chlorophenyl)-4-phenyl-N-((piperidin-1-yl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-thiocarboxamide (77.6 gram, 63 % yield).
40

Part B: To a stirred solution of 3-(4-chlorophenyl)-4-phenyl-N-((piperidin-1-yl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-thiocarboxamide (30 gram, 64.9 mmol) in acetone (1 L) is added triethylamine (18.0 mL, 130 mmol). To the resulting yellow solution is added methyl iodide (9.12 g, 64 mmol) and the resulting solution is stirred

for 16 hours at room temperature. The formed precipitate is removed by filtration. The filtrate is washed with water, concentrated *in vacuo* to give a yellow solid. Recrystallisation from MTBE gives 3-(4-chlorophenyl)-N-((piperidin-1-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester (27.9 gram, 90% yield). MP: 192-194 °C.

In an analogous manner the compounds having formula (Ib) listed below have been prepared:

- 10 36. 3-(4-Chlorophenyl)-N-((dimethylamino)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. MP: 159-160 °C.
37. 3-(4-Chlorophenyl)-N-((diethylamino)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. MP: 141-143 °C.
38. 3-(4-Chlorophenyl)-4-phenyl-N-((1,2,3,4-tetrahydroisoquinolin-2-yl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. MP: 143-145 °C.
- 15 39. 3-(4-Chlorophenyl)-N-(((ethyl)phenylamino)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. MP: 143-146 °C.
40. 3-(4-Chlorophenyl)-N-((diethylamino)sulfonyl)-4-hydroxy-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. Amorphous.
- 20 41. 3-(4-Chlorophenyl)-N-((diethylamino)sulfonyl)-4-(pyridin-4-yl)-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. Amorphous.
42. 3-(4-Chlorophenyl)-N-((piperidin-1-yl)sulfonyl)-4-(3-(trifluoromethyl)phenyl)-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. Amorphous.
43. 3-(4-Chlorophenyl)-N-((dimethylamino)sulfonyl)-4-(3-(trifluoromethyl)phenyl)-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. Amorphous.
- 25 44. 3-(4-Chlorophenyl)-N-(((ethyl)methylamino)sulfonyl)-4-(pyridin-3-yl)-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. MP: 133-136 °C.
45. 3-(4-Chlorophenyl)-N-((piperidin-1-yl)sulfonyl)-4-(pyridin-3-yl)-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. MP: 182-185 °C.
- 30 46. 3-(4-Chlorophenyl)-N-((morpholin-4-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. MP: 202-204 °C.
47. 3-(4-Chlorophenyl)-4-(2-fluorophenyl)-N-((morpholin-4-yl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. MP: 205-207 °C.
48. 3-(4-Chlorophenyl)-4-(2-fluorophenyl)-N-((piperidin-1-yl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. MP: 196-198 °C.
- 35 49. 3-(4-Chlorophenyl)-4-(2-fluorophenyl)-N-((dimethylamino)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. MP: 181-183 °C.
50. 3-(4-Chlorophenyl)-4-(2,6-difluorophenyl)-N-((morpholin-4-yl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. MP: 231-233 °C.
- 40 51. 3-(4-Chlorophenyl)-4-(2,6-difluorophenyl)-N-((piperidin-1-yl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. MP: 221-225 °C.

52. 3-(4-Chlorophenyl)-4-(2,6-difluorophenyl)-N-((dimethylamino)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. MP: 181-185°C.
53. 3-(4-Chlorophenyl)-N-((1,1-dioxidothiomorpholin-4-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. MP: 216-217 °C.
- 5 54. 3-(5-Chlorothien-2-yl)-N-((diethylamino)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. Amorphous.

Example 55**3-(4-Chlorophenyl)-N-methyl-4-phenyl-N'-((piperidin-1-yl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carboxamidine**

- 5 To a cooled mixture (< 0 °C) of 3-(4-chlorophenyl)-N-((piperidin-1-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboximidioic acid methyl ester (10.0 gram, 21 mmol) in methanol (75 mL) is added cold methylamine (15 mL). The resulting mixture is allowed to attain room temperature and stirred for 3 hours at 50 °C. After cooling to room temperature the mixture is concentrated *in vacuo*, dissolved in
10 dichloromethane, washed twice with water, dried over Na₂SO₄, filtered and concentrated *in vacuo*. Subsequent flash chromatography (EtOAc/MeOH/NH₄OH (25 % aq.) = 95/5/0.5 (v/v)), followed by recrystallisation from diisopropyl ether gives 3-(4-chlorophenyl)-N-methyl-4-phenyl-N'-((piperidin-1-yl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carboxamidine (7.87 gram, 81 % yield) as a white solid. MP: 175-177 °C.

15

In an analogous manner the compounds having formula (Ia) listed below - including those in table 1 - have been prepared:-

- 5 56. 3-(4-Chlorophenyl)-N-cyclopropyl-4-phenyl-N'-((piperidin-1-yl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 142-144 °C.
20 57. 3-(4-Chlorophenyl)-N'-((diethylamino)sulfonyl)-N-methyl-4-hydroxy-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 180-182 °C.
58. 3-(5-Chlorothien-2-yl)-N'-((diethylamino)sulfonyl)-N-methyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 122-123 °C.
25 59. 3-(4-Chlorophenyl)-N'-((dimethylamino)sulfonyl)-N-isopropyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 169-170 °C.
60. 3-(4-Chlorophenyl)-N'-((dimethylamino)sulfonyl)-N-(1-methylpiperidin-4-yl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 144-146 °C.
30 61. 3-(4-Chlorophenyl)-N-cyclopropyl-N'-((diethylamino)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 150-151 °C.
62. 3-(4-Chlorophenyl)-N'-((diethylamino)sulfonyl)-N-ethyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 116-119 °C.
63. 3-(4-Chlorophenyl)-N'-((diethylamino)sulfonyl)-N,N-dimethyl-4-hydroxy-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 135-137 °C.
35 64. N'-((Diethylamino)sulfonyl)-N,N-dimethyl-3-(4-fluorophenyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 159-160 °C.
65. 3-(4-Chlorophenyl)-N'-((diethylamino)sulfonyl)-N-isopropyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 81-85 °C.
40 66. 3-(4-Chlorophenyl)-N'-((dimethylamino)sulfonyl)-N-ethyl,N-methyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. Amorphous.
67. 3-(4-Chlorophenyl)-N-ethyl,N-methyl-N'-((piperidin-1-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 178 °C.
68. 3-(4-Chlorophenyl)-N'-((diethylamino)sulfonyl)-N-ethyl-4-hydroxy-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 162-165 °C.
45 69. 3-(4-Chlorophenyl)-N-methyl-N'-((1,2,3,4-tetrahydroisoquinolin-2-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. Amorphous.
70. 3-(4-Chlorophenyl)-N'-((ethyl)phenylamino)sulfonyl)-N-methyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 145-147 °C.

71. N'-((Diethylamino)sulfonyl)-3-(4-chlorophenyl)-N-methyl-4-(pyridin-4-yl)-4,5-dihydro-1H-pyrazole-1-carboxamide. MP: 109-111 °C.
72. 3-(4-Chlorophenyl)-N'-((dimethylamino)sulfonyl)-N-methyl-4-(pyridin-3-yl)-4,5-dihydro-1H-pyrazole-1-carboxamide. MP: 157-159 °C.
- 5 73. 3-(4-Chlorophenyl)-N'-((diethylamino)sulfonyl)-N-methyl-4-(pyridin-3-yl)-4,5-dihydro-1H-pyrazole-1-carboxamide. MP: 85-89 °C.
74. 3-(4-Chlorophenyl)-N'-((dimethylamino)sulfonyl)-N-methyl-4-(pyridin-4-yl)-4,5-dihydro-1H-pyrazole-1-carboxamide. MP: 178-182 °C.
- 10 75. 3-(4-Chlorophenyl)-N-methyl-N'-((piperidin-1-yl)sulfonyl)-4-(3-(trifluoromethyl)phenyl)-4,5-dihydro-1H-pyrazole-1-carboxamide. MP: 168-170 °C.
76. 3-(4-Chlorophenyl)-N'-((dimethylamino)sulfonyl)-N-methyl-4-(3-(trifluoromethyl)phenyl)-4,5-dihydro-1H-pyrazole-1-carboxamide. MP: 65-68 °C.
77. 3-(4-Chlorophenyl)-N'-((ethyl)methylamino)sulfonyl)-N-methyl-4-(pyridin-3-yl)-4,5-dihydro-1H-pyrazole-1-carboxamide. MP: 125-128 °C.
- 15 78. 3-(4-Chlorophenyl)-N-methyl-N'-((piperidin-1-yl)sulfonyl)-4-(pyridin-3-yl)-4,5-dihydro-1H-pyrazole-1-carboxamide. MP: 174-177 °C.
79. 3-(4-Chlorophenyl)-4-(2,6-difluorophenyl)-N-methyl-N'-((morpholin-4-yl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carboxamide. MP: 223-235 °C.
- 20 80. 3-(4-Chlorophenyl)-4-(2,6-difluorophenyl)-N'-((dimethylamino)sulfonyl)-N-methyl-4,5-dihydro-1H-pyrazole-1-carboxamide. MP: 214-216 °C.
81. 3-(4-Chlorophenyl)-4-(2,6-difluorophenyl)-N-methyl-N'-((piperidin-1-yl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carboxamide. MP: 260-263 °C.
82. 3-(4-Chlorophenyl)-4-(3-fluorophenyl)-N-methyl-N'-((piperidin-1-yl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carboxamide. MP: 170 °C.
- 25 83. 3-(4-Chlorophenyl)-4-(2-fluorophenyl)-N-methyl-N'-((piperidin-1-yl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carboxamide. MP: 223-225 °C.
84. 3-(4-Chlorophenyl)-N'-((dimethylamino)sulfonyl)-4-(2-fluorophenyl)-N-methyl-4,5-dihydro-1H-pyrazole-1-carboxamide. MP: 173-175 °C.
85. 3-(4-Chlorophenyl)-N'-((dimethylamino)sulfonyl)-4-(3-fluorophenyl)-N-methyl-4,5-dihydro-1H-pyrazole-1-carboxamide. MP: 110 °C.
- 30 86. 3-(4-Chlorophenyl)-4-(2-fluorophenyl)-N-methyl-N'-((morpholin-4-yl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carboxamide. MP: 165-168 °C.
87. 3-(4-Chlorophenyl)-N'-((1,1-dioxidothiomorpholin-4-yl)sulfonyl)-N-methyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamide. MP: 268-271 °C.
- 35 88. 3-(4-Chlorophenyl)-N'-((4-hydroxypiperidin-1-yl)sulfonyl)-N-methyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamide. MP: 80 °C.

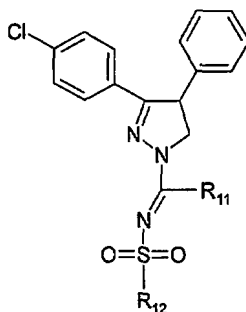


Table 1

Example:	R ₁₁	R ₁₂	MP (°C)	Salt form
89:	4-Methyl-1,4-diazepan-1-yl	Dimethylamino	197-200	0.5 Fumarate
90:	1,4-Diazepan-1-yl	Piperidin-1-yl	Amorphous	
91:	1,4-Diazepan-1-yl	Dimethylamino	Amorphous	
92:	4-Methyl-1,4-diazepan-1-yl	Piperidin-1-yl	159-164	

93:	4-Methylpiperazin-1-yl	Dimethylamino	191-193	
-----	------------------------	---------------	---------	--

Example 94

5 **3-(4-Chlorophenyl)-N-((4-methylpiperazin-1-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester**

Part A: A stirred mixture of 3-(4-chlorophenyl)-4-phenyl-4,5-dihydro-1H-pyrazole (3.21 gram, 11.3 mmol), [(4-methylpiperazin-1-yl)sulfonyl]dithioimido-carbonic acid dimethyl ester (3.08 gram, 12.0 mmol) and pyridine (25 mL) is heated at 100 °C for
 10 24 hours in a nitrogen atmosphere. After cooling to room temperature the mixture is concentrated *in vacuo*, water is added and the resulting mixture is extracted with dichloromethane. The dichloromethane extract is washed twice with water, dried over Na₂SO₄, filtered and concentrated *in vacuo*. Subsequent flash chromatographic purification gives 3-(4-chlorophenyl)-N-((4-methylpiperazin-1-yl)sulfonyl)-4-phenyl-
 15 4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester (4.24 gram, 76 % yield) as an amorphous solid. (*R_f* ~ 0.1, EtOAc/methanol = 95/5 (v/v)).

In an analogous manner the compounds having formula (Ib) listed below have been prepared:

20

95. 3-(4-Chlorophenyl)-N-(((2-(dimethylamino)ethyl)ethylamino)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester.
 MP: 158 °C.

96. N-((Diethylamino)sulfonyl)-3-(4-fluorophenyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. Amorphous.
 25 *R_f* ~ 0.4 (MTBE).

97. 3-(4-Chlorophenyl)-N-([(1,4']bipiperidin-1'-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. MP: 245 °C.

98. 3-(4-Chlorophenyl)-N-(((1-methylpiperidin-4-yl)methylamino)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. Oil. *R_f* ~ 0.15
 30 (methanol/dichloromethane = 5/95 (v/v)).

99. 3-(4-Chlorophenyl)-N-((4-methyl-1,4-diazepan-1-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. Amorphous.
 35 *R_f* ~ 0.10 (methanol/dichloromethane = 5/95 (v/v)).

Example 100

(-)-(4S)-3-(4-Chlorophenyl)-N-methyl-4-phenyl-N'-((piperidin-1-yl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carboxamidine

(-)-(4S)-3-(4-Chlorophenyl)-N-methyl-4-phenyl-N'-((piperidin-1-yl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carboxamidine (3.8 gram, 8.3 mol)) ([α_D²⁵] = -139 °, c = 0.006, MeOH) was obtained as an amorphous solid via chiral chromatographic separation of racemic
 40 3-(4-chlorophenyl)-N-methyl-4-phenyl-N'-((piperidin-1-yl)sulfonyl)-4,5-

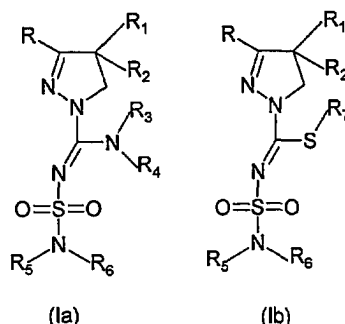
dihydro-1H-pyrazole-1-carboxamidine (7.87 gram, 17.1 mmol) using a chiral stationary phase Chiralpak AD. The mobile phase consisted of methanol/diethylamine = 999/1 (v/v).

- 5 In an analogous manner the optically pure compounds listed below have been prepared from the corresponding racemates:

101. (-)-(4S)-3-(4-Chlorophenyl)-N'-((diethylamino)sulfonyl)-N-methyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine (Chiral stationary phase: Chiralcel OD). Mobile phase consisted of hexane/2-propanol = 80/20 (v/v). ($[\alpha]^{25}_D$) = -147 °, c = 0.01, MeOH). Amorphous.
- 5 102. (-)-(4S)-3-(4-Chlorophenyl)-N'-((dimethylamino)sulfonyl)-N-methyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine (Chiral stationary phase: Chiralpak AD). The mobile phase consisted of methanol/diethylamine = 999/1 (v/v). ($[\alpha]^{25}_D$) = -171 °, c = 0.005, MeOH). Amorphous.
- 10 103. (-)-(4S)-3-(4-Chlorophenyl)-N-methyl-N'-((morpholin-4-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. ($[\alpha]^{25}_D$) = -144 °, c = 0.01, MeOH). (Chiral stationary phase: Chiralpak AD). The mobile phase consisted of ethanol. Amorphous.

Claims

1. Compounds of the general formulas (Ia) or (Ib)



wherein

- R and R₁ independently represent phenyl, thienyl or pyridyl which groups may be substituted with 1, 2 or 3 substituents Y, which can be the same or different, from the group C₁₋₃-alkyl or alkoxy, hydroxy, halogen, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, nitro, amino, mono- or dialkyl (C₁₋₂)-amino, mono- or dialkyl (C₁₋₂)-amido, (C₁₋₃)-alkyl sulfonyl, dimethylsulfamido, C₁₋₃-alkoxycarbonyl, carboxyl, trifluoromethylsulfonyl, cyano, carbamoyl, sulfamoyl and acetyl, or R and/or R₁ represent naphthyl,
- R₂ represents hydrogen, hydroxy, C₁₋₃-alkoxy, acetyloxy or propionyloxy,
- R₃ represents a hydrogen atom or a branched or unbranched C₁₋₈ alkyl group or a C₃₋₇ cycloalkyl group which alkyl group or cycloalkyl group may be substituted with a hydroxy group,
- R₄ represents a hydrogen atom or a branched or unbranched C₁₋₈ alkyl, C₃₋₈ cycloalkyl, C₂₋₁₀ heteroalkyl, C₃₋₈ nonaromatic heterocycloalkyl or C₄₋₁₀ nonaromatic heterocycloalkyl-alkyl moiety which moieties may contain one or more heteroatoms from the group (O, N, S), which moieties may be substituted with a keto group, trifluoromethyl group, C₁₋₃ alkyl group, hydroxy, amino, monoalkylamino, or dialkylamino group or a fluoro atom, or R₄ represents an amino, hydroxy, phenoxy or benzyloxy group or R₄ represents a branched or unbranched C₁₋₈ alkoxy, C₃₋₈ alkenyl, C₅₋₈ cycloalkenyl or C₆₋₉ cycloalkenylalkyl group which groups may contain a sulphur, nitrogen or oxygen atom, a keto group or -SO₂- group which C₁₋₈ alkoxy, C₃₋₈ alkenyl, C₅₋₈ cycloalkenyl or C₆₋₉ cycloalkenylalkyl groups may be substituted with a hydroxy group, a trifluoromethyl group, an amino group, a monoalkylamino group or dialkylamino group or a fluoro atom, or R₄ represents a phenyl, benzyl, pyridyl, thienyl, pyridylmethyl or phenethyl group wherein the aromatic rings may be substituted with 1, 2 or 3 of the substituents Y, wherein Y has the meaning as indicated above, or

5 R₄ represents a group NR₈R₉ with the proviso that R₃ represents a hydrogen atom or a methyl group and wherein R₈ and R₉ are the same or different and represent C₁₋₄ alkyl or C₂₋₄ trifluoroalkyl or R₈ and R₉ - together with the nitrogen atom to which they are bonded - form a saturated or un-saturated heterocyclic moiety having 4 to 8 ring atoms which heterocyclic moiety may contain an oxygen or sulphur atom or a keto group or -SO₂- group or an additional nitrogen atom, which saturated or unsaturated heterocyclic moiety may be substituted with a C₁₋₄ alkyl group or

10 R₃ and R₄ - together with the nitrogen atom to which they are bonded - form a saturated or unsaturated, monocyclic or bicyclic heterocyclic moiety having 4 to 10 ring atoms, which heterocyclic moiety may contain one or more atoms from the group (O, N, S) or a keto group or -SO₂- group, which moiety may be substituted with a C₁₋₄ alkyl, hydroxyalkyl, phenyl, thienyl, pyridyl, amino, monoalkylaminoalkyl, dialkylaminoalkyl, monoalkylamino, dialkylamino, aminoalkyl, azetidiny, pyrrolidinyl, piperidinyl or hexahydro-1H-azepinyl group,

15 - R₅ and R₆ independently of each other represent a hydrogen atom or a branched or unbranched C₁₋₈ alkyl or alkenyl group which groups may contain one or more heteroatoms from the group (O, N, S), a keto group or a -SO₂- group and which groups may be substituted with a hydroxy or amino group, or R₅ and R₆ independently of each other represent a C₃₋₈ cycloalkyl group or C₃₋₈ cycloalkenyl group which may contain one or more ring heteroatoms from the group (O, N, S) or the -SO₂- group and which groups may be substituted with a hydroxy group, alkyl (C₁₋₃), the -SO₂- group, the keto group, amino group, monoalkylamino group (C₁₋₃) or dialkylamino group (C₁₋₃), or

25 R₅ represents a naphthyl group or a phenyl group which phenyl group may be substituted with 1, 2 or 3 substituents Y wherein Y has the meaning as described hereinabove, with the proviso that R₆ represents a hydrogen atom, or a branched or unbranched alkyl group (C₁₋₅) which alkyl group may contain one or more heteroatoms from the group (O, N, S) or the -SO₂- group and which alkyl group may be substituted with a hydroxy, keto or amino group, or

30 R₅ and R₆ - together with the nitrogen atom to which they are bonded - form a monocyclic, bicyclic or tricyclic alkyl or alkenyl group which may contain ring heteroatoms from the group (O, N, S), the keto or the SO₂ group and which monocyclic, bicyclic or tricyclic alkyl or alkenyl group may be substituted with a hydroxy group, alkyl (C₁₋₃) group, SO₂ group, keto group, amino group, monoalkylamino group (C₁₋₃), dialkylamino group

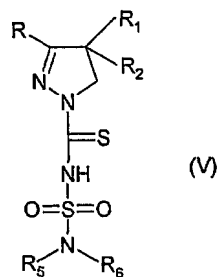
35 (C₁₋₃), pyrrolidinyl group or piperidinyl group, which monocyclic, bicyclic or tricyclic alkyl or alkenyl group may contain an annelated phenyl group which annelated phenyl group may be substituted with 1 or 2 substituents Y, wherein Y has the meaning as described herein above,

40 - R₇ represents branched or unbranched C₁₋₃ alkyl.

and tautomers, stereoisomers, prodrugs and salts thereof.

2. Pharmaceutical compositions containing a pharmacologically active amount of at least one compound as claimed in claim 1 as an active component.
- 5 3. Method of preparing pharmaceutical compositions as claimed in claim 2 characterized in that a compound as claimed in claim 1 is brought in a form suitable for administration.
- 10 4. Process for the preparation of compounds having formula (Ib), characterized in that a compound is prepared wherein R, R₁₋₂, R₅₋₆ and R₇ have the meanings given in claim 1 by
- 15 1) reacting a compound having formula (III) with a compound having formula (IV) to give a compound of the formula (V) which is reacted with a compound of the formula R₇-X, or
- 20 2) reacting a compound having formula (III) with a compound having formula (IX).
5. Process for the preparation of compounds having formula (Ia), characterized in that a compound is prepared wherein R and R₁₋₆ have the meanings given in claim 1 by
- 25 1) reacting a compound having formula (Ib), with an amine of the formula HNR₃R₄, or
- 30 2) reacting a compound having formula (V) with an amine of the formula HNR₃R₄ in the presence of a mercury (II) salt, or
- 35 3) reacting a compound having formula (III) with a compound of the formula (VI) to give a compound of the formula (VII) which is reacted with a halogenating agent to give a compound of the formula (VIII) which is reacted with an amine of the formula HNR₃R₄.
6. Compounds of the general formula (V)

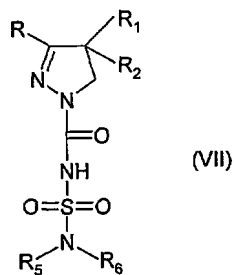
23



wherein R, R₁, R₂, R₅ and R₆ have the meanings given in claim 1.

5

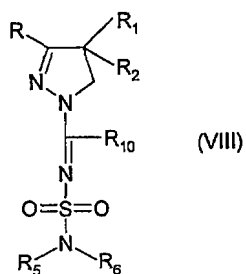
7. Compounds of the general formula (VII)



10

wherein R, R₁, R₂, R₅ and R₆ have the meanings given in claim 1.

8. Compounds of the general formula (VIII)



15

wherein R, R₁, R₂, R₅ and R₆ have the meanings given in claim 1 and wherein R₁₀ represents a halogen atom.

20

9. Use of a compound as claimed in claim 1 for the preparation of a pharmaceutical composition for the treatment of disorders involving cannabinoid neurotransmission.

10. Use as claimed in claim 9 characterised in that said disorders are psychiatric disorders such as psychosis, anxiety, depression, attention deficits, memory disorders, cognitive disorders, appetite disorders, obesity, addiction, appetite, drug dependence and neurological disorders such as
- 5 neurodegenerative disorders, dementia, dystonia, muscle spasticity, tremor, epilepsy, multiple sclerosis, traumatic brain injury, stroke, Parkinson's disease, Alzheimer's disease, epilepsy, Huntington's disease, Tourette's syndrome, cerebral ischaemia, cerebral apoplexy, craniocerebral trauma, stroke, spinal cord injury, neuroinflammatory disorders, plaque
- 10 sclerosis, viral encephalitis, demyelination related disorders, as well as for the treatment of pain disorders, including neuropathic pain disorders, and other diseases involving cannabinoid neurotransmission, including the treatment of septic shock, glaucoma, cancer, diabetes, emesis, nausea, asthma, respiratory diseases, gastrointestinal disorders, gastric ulcers,
- 15 diarrhoea and cardiovascular disorders.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 02/10435

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 .. A61K31/415 C07D231/06 C07D401/12 A61K31/4155 A61K31/4725 C07D401/04		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 7 C07D A61K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 01 70700 A (SOLVAY PHARMACEUTICALS B V) 27 September 2001 (2001-09-27) see the formula (i) definition for Aa, and formulae IX,VII and X (claims 8-10) ---	1-10
A	US 5 624 941 A (BARTH FRANCIS ET AL) 29 April 1997 (1997-04-29) the whole document ---	1-10
A	US 4 070 365 A (VAN DAALEN JAN JOHANNES ET AL) 24 January 1978 (1978-01-24) the whole document --- <div style="text-align: center;">-/--</div>	1-10
<div style="display: flex; justify-content: space-between;"> <input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex. </div>		
<div style="display: flex;"> <div style="flex: 1;"> <p>* Special categories of cited documents:</p> <p>*A* document defining the general state of the art which is not considered to be of particular relevance</p> <p>*E* earlier document but published on or after the international filing date</p> <p>*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>*O* document referring to an oral disclosure, use, exhibition or other means</p> <p>*P* document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="flex: 1;"> <p>*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>* & * document member of the same patent family</p> </div> </div>		
Date of the actual completion of the international search <div style="text-align: center;">22 November 2002</div>		Date of mailing of the international search report <div style="text-align: center;">29/11/2002</div>
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer <div style="text-align: center;">Scruton-Evans, I</div>

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 02/10435

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>PERTWEE R G: "PHARMACOLOGY OF CANNABINOID RECEPTOR LIGANDS" CURRENT MEDICINAL CHEMISTRY, BENTHAM SCIENCE PUBLISHERS BV, BE, vol. 6, no. 8, August 1999 (1999-08), pages 635-664, XP000923352 ISSN: 0929-8673 cited in the application see page 641</p> <p style="text-align: center;">---</p>	1-10
A	<p>WO 00 46209 A (SANOFI SYNTHELABO ;BARTH FRANCIS (FR); CAMUS PHILIPPE (FR); MARTIN) 10 August 2000 (2000-08-10) the whole document</p> <p style="text-align: center;">-----</p>	1-10

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 02/10435

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0170700	A	27-09-2001	AU 4250101 A WO 0170700 A1 US 2001053788 A1	03-10-2001 27-09-2001 20-12-2001
US 5624941	A	29-04-1997	FR 2692575 A1 FR 2713224 A1 FR 2713225 A1 AT 149489 T AU 4143893 A BR 1100409 A3 BR 9302435 A CA 2098944 A1 CZ 9301172 A3 DE 69308395 D1 DK 576357 T3 EP 0576357 A1 ES 2101258 T3 FI 932891 A GR 3023535 T3 HU 64526 A2 IL 106099 A JP 3238801 B2 JP 6073014 A MX 9303664 A1 NO 932296 A NZ 247961 A RU 2119917 C1 SK 65493 A3 ZA 9304511 A AT 154012 T AU 685518 B2 AU 7899994 A BR 1100984 A3 CA 2136893 A1 CN 1110968 A , B CZ 9403016 A3 DE 69403614 D1 DE 69403614 T2 DK 656354 T3 EP 0656354 A1 ES 2105575 T3 FI 945690 A GR 3024470 T3 HK 1000599 A1 HU 71498 A2 IL 111719 A JP 3137222 B2 JP 7309841 A JP 2001026541 A NO 944625 A NZ 270025 A PL 306067 A1 RU 2141479 C1 SG 68570 A1	24-12-1993 09-06-1995 09-06-1995 15-03-1997 06-01-1994 13-10-1999 11-01-1994 24-12-1993 16-03-1994 10-04-1997 15-09-1997 29-12-1993 01-07-1997 24-12-1993 29-08-1997 28-01-1994 15-07-1998 17-12-2001 15-03-1994 31-01-1994 27-12-1993 28-08-1995 10-10-1998 02-02-1994 22-02-1994 15-06-1997 22-01-1998 15-06-1995 14-03-2000 21-06-1995 01-11-1995 14-06-1995 10-07-1997 22-01-1998 29-12-1997 07-06-1995 16-10-1997 03-06-1995 28-11-1997 09-04-1998 28-11-1995 28-10-1999 19-02-2001 28-11-1995 30-01-2001 06-06-1995 26-09-1995 12-06-1995 20-11-1999 20-06-2000
US 4070365	A	24-01-1978	NL 7409433 A AR 223449 A1 AT 359775 B	14-01-1976 31-08-1981 25-11-1980

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 02/10435

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 4070365	A		AT 508277 A	15-04-1980
			AT 342585 B	10-04-1978
			AT 529175 A	15-08-1977
			AU 501280 B2	14-06-1979
			AU 8285075 A	13-01-1977
			BE 831232 A1	12-01-1976
			BR 7504413 A	06-07-1976
			CA 1075242 A1	08-04-1980
			CH 624675 A5	14-08-1981
			CS 188962 B2	30-03-1979
			DD 122775 A5	05-11-1976
			DE 2529689 A1	29-01-1976
			DK 310975 A ,B,	13-01-1976
			EG 11880 A	30-09-1978
			ES 439292 A1	16-02-1977
			FR 2277827 A1	06-02-1976
			GB 1514285 A	14-06-1978
			HU 178320 B	28-04-1982
			IE 41836 B1	09-04-1980
			IL 47676 A	31-01-1979
			IT 1044358 B	20-03-1980
			JP 1368569 C	11-03-1987
			JP 51041358 A	07-04-1976
			JP 61023162 B	04-06-1986
			OA 5057 A	31-12-1980
			PL 105891 B1	30-11-1979
			PL 193676 A1	17-07-1978
			SE 419644 B	17-08-1981
			SE 7507868 A	13-01-1976
			US 4156007 A	22-05-1979
			YU 176475 A1	30-06-1982
			ZA 7504203 A	23-02-1977
WO 0046209	A	10-08-2000	FR 2789078 A1	04-08-2000
			FR 2789079 A1	04-08-2000
			AU 2298900 A	25-08-2000
			BG 105749 A	28-02-2002
			BR 0007895 A	30-10-2001
			CN 1346349 T	24-04-2002
			CZ 20012697 A3	17-10-2001
			EE 200100399 A	15-10-2002
			EP 1150961 A1	07-11-2001
			WO 0046209 A1	10-08-2000
			HR 20010564 A1	31-08-2002
			NO 20013736 A	28-09-2001
			NZ 512886 A	25-10-2002
			SK 10872001 A3	03-12-2001
			TR 200102054 T2	21-05-2002
			US 6432984 B1	13-08-2002